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| 10/733,685 | 12/10/2003 | Douglas T. Gjerd | P004.210 | 9021 |
| 55130 | 7590 | 09/05/2007 | | |
| PHYNEXUS, INC. 3670 CHARTER PARK DRIVE SAN JOSE, CA 95136 | | | EXAMINER GAKH, YELENA G | |
| | | | ART UNIT 1743 | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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|------------------------------|--|---|--|
| Office Action Summary | Application No. 10/733,685 | Applicant(s) GJERDE, DOUGLAS T. | |
| | Examiner Yelena G. Gakh, Ph.D. | Art Unit 1743 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>02/17/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Objections

1. Claim 15 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The parent claim recites in step h) "removing the silanol titration solution from the silica surface, along with substantially all of the titration reagent that has not bound to reactable silanol groups", which covers the subject matter of claim 15.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-7 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the titration reagent, which is small enough such that the binding of a first titration reagent molecule to a reactable silanol group does not substantially hinder any other reactable silanol group, does not reasonably provide enablement for the titration reagent, which does not meet this requirement. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not enable any person of ordinary skill in the art to measure the concentrations of reactable silanol groups on a silica surface by titrating the surface with titration solution comprising large molecules that hinder neighbor silanol groups from interacting with the titration reagent, since the concentration will not be determined properly.

Claims 1-2, 5-9 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the titration reagent, which binds to reactable silanol groups with known binding, does not reasonably provide enablement for the titration reagent, which does not have the known binding stoichiometry. The specification does not enable any

Art Unit: 1743

person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not enable any person of ordinary skill in the art to measure the concentrations of reactable silanol groups on a silica surface by titrating the surface with titration solution if the binding stoichiometry of the titration reagent to the reactable silanole groups is not known.

Claims 12 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for benzyltrimethylammonium, does not reasonably provide enablement for other titration reagent comprising chromophore. The specification is silent regarding other titration reagents, which are chromophores and meet all requirements of the titration reagent for quantitative measurement of the concentration of reactable silanol groups on a silica surface. It would have been undue experimentation for any routineer in the art to search for other titration reagents comprising chromophores, which would satisfy these requirements.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites in step h) "a silanol group", which obviously should be replaced with "the silanol groups", since the titration reagent binds to silanol groups, rather than just one silanol group. Claim 1 further recites in step i) "the bound detection reagent", which does not have an antecedent basis, since only "titration reagent" was previously recited in the claim. The claim further recites, "optionally eluting the bound detection reagent from the silica surface". It is not apparent, as to how this step can be performed. How can the bound detection reagent be eluted, if it is bound to the silica surface? Should the surface first be treated with a reagent, which breaks the binding between the reagent and the surface? The same problem exists for claims 12 and 14.

Claim 8 is not clear regarding the recitation for the second titration reagent. Which "second titration reagent" is meant in the claim? From the subject matter of the claim it appears that this should be first and second "titration reagent *molecule*", which reacts with the silanol

Art Unit: 1743

group and which should not hinder the reaction of the second titration reagent *molecule* with another silanol group. If this is correct, the examiner suggests adding the word "molecule" to the expression "first titration reagent".

From claim 12 it is not apparent, whether the titration reagent is a combination of the titrating compound and an additional chromophore, or that titration reagent is a chromophore. If the chromophore is a separate compound, it is not apparent, as to how it is related to titration of the silanol groups by the titration reagent. If in fact the titration reagent is a chromophore, it should be indicated so in the claim to remove ambiguity of the claim interpretation.

Claim 16 is not clear. It is not apparent, if the titration reagent comprises two separate molecules - a quaternary alkyl ammonium group and a UV chromophore, and if it does, it is not apparent, as to how such titration reagent works.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. **Claims 1-5 and 8-9** are rejected under 35 U.S.C. 102(b) as being anticipated by Antakli et al. (Chromatographia, 1987).

Antakli teaches "determination of the concentrations of silanol groups by a chemical reaction with methyllithium and GC measurements of evolved methane" (Title). Silanol groups belong to chromatographic material surfaces (coating of the capillary channel). Methyllithium, which is a relatively small molecule (MW < 500), stoichiometrically binds to silanol groups in 1:1 ratio. Excess of the reagent is washed away with air (see page 768, left column). The concentration of reactable silanol groups is determined from the quantity of evolved methane, which is formed from the bound reagent.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. **Claim 6** is rejected under 35 U.S.C. 103(a) as being unpatentable over Antakli.

While Antakli does not specifically disclose that the silica surface comprises the channel surface of a capillary, chromatographic capillary columns coated with silica are conventional in the art, and therefore it would have been obvious for any person of ordinary skill in the art to apply Antakli's method specifically for the chromatographic capillary with silica inner surface.

10. **Claims 7, 10, 14** are rejected under 35 U.S.C. 103(a) as being unpatentable over Antakli in view of the prior art disclosed by Possemiers et al. (J. Chem. Soc., Faraday Trans., 1996).

Antakli does not disclose ammonium derivatives (e.g. quaternary ammonium alkyl salts) as titration reagents.

Possemiers indicates in the description of the prior art that extensive studies of binding of ammonia to silanol groups on silica surfaces have been conducted, and the conclusion was drawn that the binding occurs in 1:1 stoichiometric ratio.

It would have been obvious for any person of an ordinary skill in the art to use alkyl ammonium instead of methyl lithium for determining concentration of the reactive silanol groups on the silica surface, because it was demonstrated that ammonia participates in a reversible and therefore controllable H-binding with reactive silanol groups on the silica surface in the stoichiometric ratio of 1:1, with alkyl ammonium derivatives being easier to detect than ammonia

gas, which is released from silica surface, in order to determine the concentration of the reactive silanol groups.

Allowable Subject Matter

11. **Claims 11 and 17** would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The prior art does not teach or fairly suggest using benzyltrimethylammonium as a titration reagent for detecting concentration of silanol groups on the silica surface.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. *Sears (Anal. Chem., 1956)* teaches "determination of specific surface area of colloidal silica by titration with sodium hydroxide" (Title); *Bradley et al (Anal. Chem., 1959)* teach "determination of primary amino alkyl alkoxy silane coating on glass substrates" (Title); *Barnes et al. (Anal. Chem., 1963)* teach "diglyme as solvent in the gasometric determination of silanols by the lithium aluminum hydride method" (Title); *Miller et al. (J. Chromatogr., 1985)* teach "characterization of silanol reactivity and acidity on octadecyl-bonded chromatographic supports by ²⁹Si solid-state NMR and surface titration" (Title); *Takeuchi et al. (Anal. Chimica Acta, 1993)* teach "determination of the specific surface area of silica gel by on-column titration with hydrochloric acid".

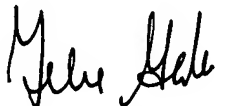
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1743

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

8/2/20079


YELENA GAKH
PRIMARY EXAMINER